REMARKS

Claims 1, 2, and 21-40 are pending in the application. Claims 3-20 have been canceled, claims 21-26, 29, and 33 have been amended, and claims 35-40 have been added. Support for the amendments can be found in the specification at, e.g., page 7, line 34, to page 8, line 14; page 9, line 35, to page 10, line 1; page 22, line 11, to page 23, line 14; and page 27, line 28, to page 28, line 13. These amendments add no new matter.

Allowable Subject Matter

At page 2 of the Office Action, the Examiner stated that claims 1, 2, and 29-32 "seem to be free of the prior art and are allowable." In view of the amendments and arguments presented herein, applicants respectfully submit that all of the pending claims are in condition for allowance.

35 U.S.C. §112, First Paragraph (Written Description)

At pages 2-6 of the Office Action, the Examiner rejected claims 3-8, 21-28, 33, and 34 as allegedly containing subject matter that was not described in the specification in such a way that one skilled in the art can reasonably conclude that applicant had possession of the claimed invention at the time of filing. According to the Examiner,

> [c]laims 21-25, 34 encompass unrelated amino acid sequences of any length and any structure, provided that they contain amino acids 10-116, 126-420, 568-660, 676-745, or 826-1004 of SEQ ID NO:2. Claims 26-28 encompass variants of SEQ ID NO:2, wherein the function of said variant is unknown, because binding to Bcl-10 is not a function.
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> The specification discloses that CARD-14 associates with Bcl-10 via the N terminal CARD domain (p.21 and p.22, first paragraph). The specification also discloses that the N-terminal CARD of CARD-14 was essential for NF-kB signaling (p.24). No disclosure however is found in the specification whether the N-terminal CARD by itself is sufficient for activating NF-kB. . . .
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> No common structural attributes that identify the claimed variants are disclosed. In addition, no common functional attributes that identify the claimed variants are disclosed , because the function of a polypeptide sequence could be abolished, even with substitution of only one amino acid of the polypeptide. . . Since the

disclosure fails to describe the common attributes or characteristics that identify members of the claimed variants, SEQ ID NO:2 alone is insufficient to describe said variants.

Claims 3-8 have been canceled, thereby obviating their rejection. Applicant respectfully traverses the rejection with respect to claims 21-28, 33, and 34

(i) Polypeptides Containing a Specific Functional Domain of CARD-14

The present application describes the identification and characterization of CARD-14, a caspase recruitment domain (CARD)-containing protein. A CARD is a protein-binding module that mediates the assembly of CARD-containing proteins into apoptosis and NF-kB signaling complexes. CARD-14 has an N-terminal CARD (at about amino acid residues 10-116 of SEQ ID NO:2), a central coiled-coil domain (at about amino acid residues 126-420 of SEQ ID NO:2) that mediates CARD-14 oligomerization, and a C-terminal tripartite domain containing a PDZ domain (at about amino acid residues 568-660 of SEQ ID NO:2), a Src homology 3 domain (SH3; at about amino acid residues 676-745 of SEQ ID NO:2), and a guanylate kinase domain (GUK; at about amino acid residues 826-1004 of SEQ ID NO:2) (see specification at page 18, lines 26-36; page 24, line 20; and page 26, lines 1-16). The PDZ, SH3, and GUK domains are found in members of the membrane-associated guanylate kinase (MAGUK) protein family, to which CARD-14 belongs. The specific amino acid sequence positions of SEQ ID NO:2 recited in each of claims 21-25 correspond, respectively, to the CARD, coiled coil domain, PDZ domain, SH3 domain, and GUK domain of CARD-14.

The precise structural definition of the polypeptide of claims 21-25 (comprising amino acid residues that correspond to the CARD, coiled coil domain, PDZ domain, SH3 domain, or GUK domain of CARD-14) allows the skilled artisan to readily envision the claimed invention and understand that applicant invented what is claimed. The polypeptides of claims 21-25 are described in the specification at, for example, page 27, lines 8-11; page 38, lines 2-5; page 42, lines 3-5; page 66, line 29, to page 67, line 30. In addition to these descriptions, a working example of a polypeptide containing the CARD of CARD-14 is described in the specification at page 20, lines 10-31. In that working example, applicant demonstrated that a polypeptide containing the CARD of CARD-14 binds specifically to the CARD of Bcl-10.

Because the claimed polypeptides contain a particular functional domain of CARD-14, the polypeptides necessarily retain the functional activity present in the recited portion of CARD-14. Polypeptides containing such functional regions of CARD-14 can be used, for example, in screening for compounds that modulate a CARD-14 activity associated with that particular region. For example, a polypeptide containing amino acids 10-116 of SEQ ID NO:2 (CARD) of CARD-14 necessarily has a Bcl-10 binding activity, and can therefore be used to screen for compounds that modulate the ability of CARD-14 to bind to Bcl-10. In another example, a polypeptide containing amino acids 126-420 of SEQ ID NO:2 (coiled coil domain) of CARD-14 necessarily has an oligomerization activity, and can therefore be used to screen for compounds that modulate the ability of CARD-14 to form oligomers. Similarly, polypeptides containing a PDZ, SH3, or GUK domain can be used to screen for modulators of those functional domains (see, e.g., page 66, line 29, to page 67, line 30).

As detailed herein, the CARD-containing polypeptides of claims 21-25 (and dependent claims 33 and 34) are amply described in the specification, both in terms of structure and associated function, such that the skilled artisan would readily understand applicant to have been in possession of the claimed invention at the time of filing of the present application. Accordingly, applicant requests that the Examiner withdraw the rejection.

(ii) Percent Identity

Claims 26-28 are drawn to a polypeptide that: (a) binds to Bcl-10; and (b) contains an amino acid sequence that is at least 85% identical to the sequence of SEQ ID NO:2. The genus of polypeptides encompassed by claims 26-28 does not have substantial variation, since all such polypeptides must have a specified activity and contain an amino acid sequence that has at least 85% identity to SEQ ID NO:2. The CARD-14 polypeptides disclosed in the specification are representative of the claimed genus because: all members of the genus contain an amino acid sequence that is highly similar to a reference sequence (SEQ ID NO:2); and the specification describes assays for identifying polypeptides that bind to Bcl-10 (such assays are described in the specification at, e.g., page 20, lines 10-25). In light of this disclosure, the skilled artisan would have concluded, at the filing of the present application, that applicant was in possession of the necessary common attributes possessed by the members of the genus.

At page 3 of the Office Action, the Examiner stated that the function of the polypeptides of claims 26-28 "is unknown, because binding to Bcl-10 is not a function." Contrary to the Examiner's assertion, applicant respectfully submits that the ability of a polypeptide to bind to another protein is indeed a biological function of the polypeptide. For example, some proteins contain a binding domain that is responsible for binding to a target protein as well as a catalytic domain that carries out a catalytic function only after a binding event has taken place. Clearly, the "binding function" is of significant importance to the biological activity of the polypeptide and can be a necessary prerequisite to a subsequent catalytic function. In another example, the skilled biologist readily understands that the ability of an antibody to bind to a target antigen is a biological function of the antibody. In fact, such a "binding function" is frequently a functional limitation recited in claims directed to antibody molecules.

The binding of CARD-14 to Bcl-10 is a requisite step in the triggering of cell signaling processes that result from the CARD-14-Bcl-10 protein-protein interaction. A person of ordinary skill in the biological arts would understand this binding event to constitute a functional activity of the CARD-14 polypeptide. Uses for the Bcl-10-binding polypeptides of claims 26-28 are detailed below in the enablement section of the present response. A person of ordinary skill in the art would clearly understand the structural and functional description of the polypeptide provided by the claims and would therefore understand applicant to have been in possession of the claimed polypeptide at the time the application was filed. Accordingly, claims 26-28 satisfy the written description requirement.

35 U.S.C. §112, First Paragraph (Enablement)

The Examiner rejected claims 26-28 as allegedly not enabled. According to the Examiner, "Applicants have not shown how to make and use the claimed polypeptide variants which are capable of functioning as that which is being disclosed."

Applicant respectfully traverses the rejection in light of the following comments. As detailed above with respect to the written description rejection, claims 26-28 are drawn to a polypeptide that: (a) binds to Bcl-10; and (b) contains an amino acid sequence that is at least 85% identical to the sequence of SEQ ID NO:2.

The specification includes extensive working examples that characterize the role of CARD-14 in cell signaling pathways involved in apoptosis and/or inflammation. In particular, applicant has demonstrated that: (1) CARD-14 selectively binds to the CARD of Bcl-10, a signaling protein that activates NF-kB through the IkB kinase complex in response to upstream stimuli (page 20, line 9, to page 22, line 9); (2) CARD-14 induces phosphorylation of Bcl-10 (page 22, line 11, to page 23, line 20); and (3) CARD-14 stimulates the activation of NF-kB (page 23, line 22, to page 24, line 15). These findings, indicate that CARD-14 functions as an upstream activator of Bcl-10 and NF-kB signaling.

In light of applicant's findings demonstrating that CARD-14 binds to Bcl-10, one of ordinary skill in the art would have been able, at the time of filing of the present application, to use the Bcl-10-binding polypeptides of claim 26-28 without undue experimentation in screening assays to identify candidate therapeutic agents that inhibit the CARD-14-Bcl-10 interaction (and thereby block cell signaling processes that result from the interaction). The specification discloses that the claimed polypeptides can be used in such screening assays and provides extensive teachings on how to carry out such screens to identify molecules that block the binding of Bcl-10 to CARD-14 (see, e.g., page 66, line 29, to page 70, line 4). In addition, the specification teaches how to make variants of SEQ ID NO:2 as well as how to evaluate the ability of such variants to bind to Bcl-10 (see, e.g., page 20, lines 10-25; and page 41, line 20, to page 42, line 30).

In light of these comments, applicant submits that one of ordinary skill in the art would have been able, at the filing of the present application, to make and use the claimed polypeptides without undue experimentation. Accordingly, applicant requests that the Examiner withdraw the rejection.